REMARKS

References to pages and lines of the text of the specification made herein correspond to those of PCT publication No. WO 01/01968 of international application No. PCT/CA00/00790, on which the above-captioned U.S. national stage application is based in accordance with 35 USC 371.

Amendments to the Claims

Applicants have amended the claims as shown above. In particular, Claims 9-39 are withdrawn in accordance with the Examiner's finality of the restriction requirement made over Applicants' traverse in the Office Action, dated April 19, 2005.

Applicants have also amended Claim 1 to delete the term "non-toxic" and, instead, to state that the method of treating obesity comprises administering "an effective amount of" a gut motility-regulating compound that is a trichothecene or derivative thereof. Support for the amendment is found in the specification (see, e.g., at page 29, lines 6-9). Accordingly, the amendment adds no new matter.

Entry of the amendments to the claims is respectfully requested.

Copies of Documents Requested by the Examiner

In the Office Action, dated April 19, 2005, the Examiner requested copies of several articles listed in an Information Disclosure Statement (IDS) and a Modified Form 1449 that were submitted by Applicants along with copies of the documents listed therein on January 29, 2003, and, thus, prior to examination on the merits. In particular the Examiner requested copies of the following documents as designated by the two-letter code of the Modified Form PTO-1449

"BA": Cubeddu et al., *Sem. Oncol., 19*: 2-13 (1992)

"CX": Rapley et al., *Lab. Anim. Sci., 38*: 5041 (1988)

"CY": Rapley et al., *Lab. Anim. Sci., 38*: 504 (1988)

"DJ": Udell et al., *Z. Naturfarsch., 44*: 660-668 (1989) ("DJ")

"DU": Yoshizawa et al., *Appl. Microbiol., 29*: 54-58 (1975) ("DU")

The Examiner mentioned that the above documents as well as documents listed in a "European search report" should be submitted in an IDS so that the documents may be considered as part of the record.

Applicants note that the citation for the CX entry of the Modified Form PTO-1449 that accompanied the IDS of January 29, 2003, is an inadvertent typographical error of the citation that is correctly provided for the CY document (see, above). The DJ citation is simply a mistaken entry on the Modified Form PTO-1449. Neither the CX nor the DJ citations appeared in the listing of documents on the IDS that accompanied the Modified Form PTO-1449 and, accordingly, copies of neither citation were submitted. Applicants apologize for any confusion to the Examiner for these two erroneous entries on the Modified Form PTO-1449.

Applicants also note that all ten (10) documents cited in the International Search Report prepared by the European Patent Office for the corresponding international application No. PCT/CA00/00790, were properly listed for consideration by the Examiner on the IDS and the Modified Form PTO-1449 that were submitted January 29, 2003.

The Patent Office acknowledged receipt of copies of all documents provided with Applicants' IDS submitted on January 29, 2003, as evidenced by Applicants' receipt of a return postcard stamped February 3, 2003 (copy of postcard enclosed as Exhibit A). In addition, when Applicants provided a true copy of their file to restore the entire missing contents of the Patent Office's file on March 3, 2004, Applicants promised to provide copies of any documents previously submitted with their IDS of January 29, 2003, upon request. Accordingly, as requested by the Examiner, Applicants provide herewith replacement copies of the following documents: BA (Cubbedu et al., 1992) at Exhibit B, CY (Rapley et al., 1988) at Exhibit C, and DU (Yoshiwaza et al., 1975) at Exhibit D.

Applicants believe that copies of all documents as originally provided with their IDS of January 29, 2003, have now been restored to the Patent Office file for consideration in this application. Applicants will, of course, provide any additional replacement copies upon request.

Restriction Requirement, Withdrawn Claims

In the Office Action, the Examiner noted that Applicants' previous response with traverse to the Restriction Requirement, issued back on July 31, 2003, was not persuasive and, therefore,

made the restriction requirement final. Accordingly, Applicants acknowledge the Examiner's making the Restriction Requirement final and that Claims 1-7 are the subject of the current Office Action.

In addition, the Examiner mentioned that new Claims 32-39, which cover a method of regulating food intake, have been withdrawn as directed to non-elected invention. In particular, the Examiner mentioned:

> "Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits." (page 3, Office Action, dated April 19, 2004).

Applicants note that submission of a Preliminary Amendment on September 25, 2003, which introduced new Claims 32-39, was not prior to any action *on the merits* of this application. Accordingly, new Claims 32-39 were properly available for consideration prior to the current pending Office Action, which is the *first* action on the merits. Moreover, as thoroughly explained throughout the specification, the methods of Claims 1-7 for treating obesity operate by regulating food intake, i.e., to reduce food intake as the result of administering a trichothecene or derivative thereof, according to the invention, to stimulate a fed pattern of gut motor activity that in turn signals satiety, i.e., the feeling of fullness, by which vertebrate individuals reduce food intake long before the brain has analyzed the nutrient content of ingested food (see, e.g., in the specification, page 3, lines 2-9; page 12, line 26 - page 13, line 26). Accordingly, Applicants respectfully submit that Claims 32-39, covering a method of regulating food intake, can and should properly be examined along with Claims 1-7.

The above comments notwithstanding, Applicants acknowledge the Examiner's finality of the Restriction Requirement and withdrawal of Claims 32-39.

The Invention

At the outset, Applicants note that contrary to the prevailing assumptions and teachings of the mycotoxin literature of the past thirty or more years, Applicants' claimed invention is based on their discovery that a variety of trichothecenes and derivative compounds surprisingly possess a pharmacological activity that is likely to have an enormous therapeutic and/or

prophylactic benefit to the health of humans and other vertebrate animals. *In particular, Applicants' disclosure shows that such compounds can act non-toxically outside the gut tissues and organs as neuroregulatory agents of a specific neural pathway defined by the enteric P_{2X1} purine receptor (i.e., the P_{2X1} purinoceptor found innervating gut tissues and organs) to modulate the pattern of contractions and relaxations in the gut tissues and organs in a manner that is comparable to the normal gut motor activity (gut motility) that occurs after an individual ingests food* (see, e.g., in the specification, at page 11, line 30 - page 12, line 9; page 15, lines 20-26; Examples 3-5, page 46, line 1 - page 60, line 29). Thus, stimulation of the "fed pattern" of gut motor activity signals satiety, i.e., the feeling of fullness, which prompts an individual to stop eating. This invention provides methods and compositions comprising a trichothecene or derivative thereof that stimulates a fed pattern of gut motility resulting in decreased food intake. Accordingly, this invention provides new methods that may be used to treat disorders of overeating and undesirable weight gain, such as obesity in humans and other vertebrate animals (see, e.g., in the specification page 16, line 5 - page 19, line 13; page 20, line 11 - page 22, line 21; Example 1, page 31, line 23 - page 41, line 10; Example 4, page 51, line 26 - page 58, line 5). Applicants made this discovery by studying the pharmacological activity of pure preparations of trichothecenes and derivatives thereof using a relatively recently developed method that permits the accurate, analytical recording *in vivo* of both components of gut motility (i.e., contractions and relaxations; simultaneously, if desired) at multiple sites in gut tissues and organs (see, e.g., page 14, line 6 - page 15, line 17, of the specification; see, also, Krantis et al., *Can. J. Physiol. Pharmacol., 7*: 894-903 (1996), of record as "CB").

Applicants' elucidation of a true, neuroregulatory, pharmacological activity of purified forms of known trichothecenes and derivative compounds described in the specification also brings into question the past assumptions made by various researchers that such compounds are the true causative agents of the toxic effects associated with ingestion of fungally contaminated crops and foods. Many toxicology studies on ingestion of trichothecenes have employed naturally or deliberately fungally contaminated cereals as the source of trichothecenes; as is clearly the case in studies described in a number of documents cited in the Office Action, e.g., Rotter et al., *J. Toxicol. Environ., 48*: 1-34 (1996) (DB); Bergsjo et al., *Vet. Res. Comm., 17*: 283-294 (1993) (AG); Friend et al., *Can. J. Anim. Sci., 66*: 765-775 (1986) (BK) (all of record).

Moreover, feed refusal and weight loss in animals that ingest trichothecenes have been viewed in the literature as prominent pathological symptoms of mycotoxin poisoning in humans and other vertebrate animals (and, particularly detrimental to the marketable weight of livestock), not as evidence of a potentially beneficial pharmacological activity (see, e.g., Arnold et al., *Fund. Appl. Toxicol., 6*: 691-696 (1986) (AC) and Friend et al. (1986), of record and cited in the Office Action). Applicants are aware of no teaching or suggestion of their claimed new use of such compounds as beneficial pharmacological agents to decrease food intake and treat obesity. Accordingly, Applicants' claimed invention is new and completely antithetical to the teachings of the documents cited in the Office Action and, indeed, the mycotoxin literature as a whole.

Rejections of Claims 1-7 under 35 USC 112, first & second paragraphs (enablement, indefiniteness)

In the Office Action, the Examiner rejected Claims 1-7 for lacking an enabling disclosure under 35 USC 112, first paragraph, and for being indefinite under 35 USC 112, second paragraph. In particular, the Examiner objected to the term "non-toxic" recited in Claim 1 and claims depending therefrom. The Examiner noted that trichothecenes have been classified as mycotoxins that have serious side effects as exemplified by Coppock et al., *Am. J. Res., 46(1)*: 169-174 (1985) ("Coppock"); Morrisey et al., *Fd. Chem. Toxic., 23(11)*: 995-999 (1985) ("Morrisey"); and Rotter et al., *J. Toxicol. Environ. Health, 48*: 1-34 (1996) ("Rotter"). Moreover, the Examiner mentioned that in view of articles such as Coppock, Morrisey, and Rotter, it is not understood how "an active toxin" can be used in a "non-toxic" amount so that the term is not clear. Applicants respectfully traverse the rejections for the reasons explained below.

As noted above, Applicants have amended Claim 1, and thereby claims depending therefrom, to delete the term "non-toxic". The term "non-toxic" was recited because Applicants recognized that any method useful for treating obesity will not employ a toxic level of any compound that provides the required beneficial pharmacological activity. As an alternative, Claim 1, as amended herein, recites language commonly employed in claims of pharmaceutical methods. Specifically, Claim 1 now clearly states that the method for treating obesity according to the invention employs "an effective amount" of a gut motility regulating compound that is a trichothecene or derivative thereof. Applicants submit that persons skilled in the art understand

that a method of treating obesity according to the invention must employ an effective amount of the compound that provides the pharmacologically beneficial activity.

Applicants respectfully submit that Coppock, Morrisey, and Rotter cannot be considered relevant to the discovery of and clear teachings and guidance provided by Applicants' specification for the claimed new use of trichothecene compounds to treat obesity. Applicants do not know the basis of the toxic effects using contaminated cereals and feed, e.g., in Rotter, but clearly other substances may be present in such crude, natural preparations. Even relatively pure preparations may contain other species, even trace substances, that alone or synergistically with other compounds may cause adverse effects (see, e.g., page 998, of Morrisey; see, also, D'Mello cited in the Office Action). Applicants have no control over the purity of compounds, preparation of animal feeds, or the health and handling of animals employed in such studies. For example, in Coppock, the four swine used in the study were cross-bred animals *randomly chosen from a commercial swine herd* (see, Materials and Methods, at page 169 of Coppock). Studies such as these that employed undefined, crude, natural preparations and/or stock animals may be subject to and provide any number of possible sources of toxins or harmful agents, including traces of naturally occurring, but unrecognized toxic substances that may have contributed to the reported pathologies. What *is* clear is that none of the documents cited in the Office Action are comparable to Applicants' disclosure that provides an accurate description of a heretofore undescribed pharmacological activity of trichothecene compounds on gut motility, that identifies the neural pathway through which such activity is effected, and that recognizes and describes beneficial uses that such pharmacologically active compounds can provide in treating disorders such as obesity.

Applicants further note that effective amounts of pharmacologically active compounds are routinely determined by persons skilled in the pharmaceutical art and tested in phased clinical trials during the process of regulatory approval when the benefit and side effects of various doses of a drug are assessed. Moreover, even when an appropriate dosing for a drug is determined and the drug approved for use, such use is often with full knowledge that one or more possible side effects may occur in some portion of the population of treated patients. In such cases, various treatments may be recommended to counteract or ameliorate such side effects that may emerge. For example, a well-known potent emetic agent, apomorphine, that was formerly used to induce

vomiting, is now currently employed to treat male impotency (see, e.g., U.S. Patent Nos. 6,306,437 and 6,436,950 in Exhibits E and F, respectively), to treat dystonia (see, e.g., Colosimo et al., *Clin. Neuropharmacol., 17*: 243-259 (1994), in Exhibit G), and to replace L-dopa to treat Parkinson's Disease patients or to treat severe motor fluctuations in Parkinson's Disease patients who have undergone chronic L-dopa therapy (see, Colosimo et al., 1994). In spite of the fact that in the new use, the apomorphine is not prepared to induce vomiting, some patients may be pretreated or contemporaneously treated as needed for the side effects of nausea and/or vomiting by using any of a large variety of known anti-emetic agents, e.g., domperidone, chlorpromazine, prochlorperazine, trimethobenzamide, and many others (see, e.g., col. 6, lines 30-63, and col. 7, lines 17-32 of US 6,306,437; col. 6, lines 35-59 of US 6,436,950; pages 243-245 of Colosimo).

Applicants respectfully submit that persons skilled in the art who have the benefit of Applicants' specification are able to clearly understand what compounds may be used according to the invention to carry out the claimed method for treating obesity. In view of the clear and detailed teachings and guidance of the specification, it is well established that it is not a function of the claims to specifically exclude possible inoperative or ineffective embodiments because the claims are commensurate with the disclosure (see, e.g., *Atlas Powder Co. v. E.I. Dupont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Dinh-Nguyen*, 492 F.2d 856, 858-859, 181 USPQ 46, 48 (CCPA 1974)).

In view of the above comments and amendments to the claims, Applicants respectfully submit that the claims are clear and definite and that the specification provides more than sufficient teachings and guidance for persons skilled in this art to carry out the claimed method as required by 35 USC 112, first and second paragraphs. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

Rejections of Claims 1-7 as Anticipated by or Obvious Over Prior Art Documents

In the Office Action, the Examiner rejected Claims 1-7 as anticipated by or, in the alternative, as obvious over the following prior art documents:

> Bergsjo (AG) in combination with Williams et al., *Arch. Environ. Contam., Toxicol., 18*: 374-387 (1989) (DR),
>
> Arnold (AC) in combination with Williams (DR), and

Friend (BK) in combination with Williams (DR).

Applicants respectfully traverse the rejections. As shown below, the documents cited by the Examiner are examples of the mycotoxin literature and only teach that trichothecenes are toxic substances that should be avoided by humans and other animals.

Bergsjo and Williams

Regarding Bergsjo and Williams, the Examiner stated:

> "Bergsjo shows that feeding pigs DON decreases body weight gain (see Abstract, page 293, last paragraph). *This is equivalent to a treatment of obesity*. Further, the effects of T-2 mycotoxins such as trichothecene is well known as an inherent property of that molecule. In the alternative, this property of trichothecenes on gastric motility is disclosed by Williams et al at page 374. Williams also draws an equivalence between clinical symptoms in humans, cattle, swine and bird. The Fusarium mycotoxin is listed and is inclusive of DON (see Bergsjo et al). As such the instant method is clearly anticipated by Bergsjo et al if the effects of gastric motility are viewed as an inherent property of that molecule. If in the alternative, it is not viewed as inherent, those of ordinary skill would expect similar decreases in weight as well as gastric motility effects in humans, cattle, pigs or birds given the disclosure of Bergsjo in view of Williams. *The treatment of obesity and effects on gastric motility produced by administration of trichothecenes such as DON would therefore be obvious in view of the teaching of Bergsjo in view of Williams*." (Office Action at page 6, emphasis added).

As shown below, whether taken alone or in combination, Bergsjo and Williams do not teach or suggest Applicants' claimed method involving the therapeutic use of trichothecene compounds or derivatives thereof to treat obesity.

Bergsjo is an example from the mycotoxin literature of a feeding study using livestock (pigs) and that classifies trichothecenes, such as deoxynivalenol (DON), as toxic compounds that can have a negative effect on the weight of livestock. The objective of the study in Bergsjo was:

> "to investigate the level at which DON originating from naturally contaminated oats would produce observable toxic effects in growing pigs." (page 284, Bergsjo).

In Bergsjo, pigs were fed mixtures of feed supplemented with various amounts of naturally contaminated oats that were used as a source of the trichothecene deoxynivalenol (DON). The oats were purchased from a private farmer whose crops had experienced "heavy *Fusarium* infestation on his harvest the preceeding year" (page 284, Bergsjo). The oats contained various other trichothecenes (page 284, Bergsjo) and "the contaminating fungal flora was dominated by *Fusarium avenaium*, *Fusarium culmorum*, and dematiaceous moulds" (page 287, Bergsjo). Clearly, the oats used in Bergsjo were not only a crude source of DON but also of various undefined compounds and organisms. The study continued until each set of animals reached 100 kg (about 5 months).

Various parameters were measured during the study with the primary focus on the effect of weight of the livestock, but always as a negative, toxic effect of DON:

> "The results of this study largely agree with the performance results from our previous investigation [citation omitted] in which we found that a DON level of 2 mg/kg of the feed significantly reduced the weight gain of growing pigs. In the present study, a dose-related decrease in daily feed intake was demonstrated at about the same dietary DON concentration (1.7 mg/kg). Differences between the two studies were the improved composition of the feed *to secure maximum feed intake and toxin exposure*, and the increased group size in this study. . . .
>
> "Several workers have reported *negative effects of DON* upon performance parameters in pigs with dietary levels from 1 mg/kg or even lower. A review of these studies was edited by Beasley (1989). Most of the studies referred to in that review were in agreement *as far as the effective toxic levels of DON are concerned*, even when experiments were performed with pigs of different age groups, provided that the mycotoxin was administered in naturally contaminated feed. Addition of isolated mycotoxin to diets has, for some reason, proved to be less efficient in causing toxic effects [citation omitted]. *The explanation may be that naturally contaminated grains frequently contain additional mycotoxins along with DON.* However, the low concentrations of the two other mycotoxins detected, 3-ac-DON and zearalenone, in the oats used in the present experiment, were not considered to be toxicologically important (Table 1)." (page 292, Bergsjo, bracketed comments and emphasis added).

The above excerpts from Bergsjo show that the only reason for feeding pigs a diet containing fungally contaminated oats was to study a toxic effect of natural mycotoxin, i.e., including DON and others present in the experimental feed, on the weight of livestock, that any observable reduction of weight of the pigs in the study was interpreted as another example of DON-mediated toxicosis, and that variations in studies are likely due to the undefined nature of naturally contaminated feed sources. Nowhere does Bergsjo indicate that any of the control or treated pigs were treated for obesity as the result of eating a diet of increasing amounts of the contaminated oats containing DON. Only Applicants' specification discloses that pure preparations of DON and other trichothecenes or derivatives thereof possess a defined beneficial pharmacological activity of inducing a fed pattern of gut motility and that such compounds may be used therapeutically to treat obesity. Accordingly, the toxic or negative effect from ingesting the contaminated oats in Bergsjo is clearly *not* equivalent to or suggestive of Applicants' claimed method of treating obesity in humans and other vertebrate animals.

Williams reviews various toxicological studies of the T-2 mycotoxin trichothecene that is described as "the principal toxic compound of *Fusarium* sp." (see, abstract, page 374, Williams). The review provides a survey of literature of the pathological properties of T-2 toxicosis:

> "Presently there is a substantial amount of information available in the literature on the occurrence and identification of T-2 mycotoxin in food residues. However, there is a lack of information on T-2 mycotoxin specially addressing gastrointestinal **complications and pathology**. An attempt is made here to consolidate such information while describing *in vivo* and *in vitro* models. Efforts were made to eliminate reported field cases where only circumstantial evidence implicated T-2 mycotoxin consumption. (pages 374-375, Williams; bold added).

Thus, it is in the context of a review of gastrointestinal complications and pathology that Williams provides various accounts of T-2 poisoning, such as:

> "Intoxication with T-2 mycotoxin results in weight loss due to diarrhea and emesis . . . ." (page 375, Williams)

and:

> "In calves, orally given 0.32-0.46 mg/kg of T-2 mycotoxin, ulcerations develop in the abomasum and rumen, and an acute enteric response with bloody feces occurs [citations omitted]. The

> calves become inappetant, dehydrated and a slight to severe weight loss was observed *respective to the toxin dose level. Clinicopathologic* changes were restricted to the higher toxin dosages . . . ." (page 380, Williams; bracket comment and emphasis added).

Applicants respectfully submit that Williams only provides persons of ordinary skill in the art with a survey of mycotoxin literature that describes various studies in which the T-2 trichothecene is viewed as the primary source of one or more pathological conditions. Nowhere does Williams teach or suggest that a trichothecene may possess a useful pharmacological activity of inducing a fed pattern of gut motility or that such a compound may be used beneficially such as in treating obesity as described in Applicants' specification. Moreover, although there appears to be no basis in either document for combining Williams with Bergsjo, even if Williams is combined with Bergsjo, Williams still fails to cure the deficiencies of Bergsjo to provide a teaching or suggestion of Applicants' claimed invention. On the contrary, when taken together, Bergsjo and Williams only teach that trichothecenes are toxic substances that should be avoided. The combination of Bergsjo and Williams does not teach or even suggest that trichothecenes may be employed to treat a disorder such as obesity. Clearly, Applicants' claimed invention is not anticipated or obvious over the combination of Bergsjo and Williams.

Arnold and Williams

In the Office Action, the Examiner also rejected the claims as anticipated by or obvious over Arnold in combination with Williams in essentially the same reasoning as that presented for the combination of Bergsjo and Williams (above):

> "Arnold et al disclose that exposure to DON causes a reduction in body weight (see, Abstract; page 695, second to last paragraph). *This is equivalent to a treatment of obesity.* Further, the effects of T-2 mycotoxins such as trichothecene is well known as an inherent property of that molecule. In the alternative, this property of trichothecenes on gastric motility is disclosed by Williams et al at page 374. Williams also draws an equivalence between clinical symptoms in humans, cattle, swine and bird. The Fusarium mycotoxin is listed and is inclusive of DON (see Arnold et al). As such the instant method is clearly anticipated by Arnold et al if the effects of gastric motility are viewed as an inherent property of that molecule. If in the alternative, it is not viewed as inherent, those of ordinary skill would expect similar decreases in weight as well as

> gastric motility effects in humans, cattle, pigs or birds given the disclosure of Arnold et al view of Williams. *The treatment of obesity and effects on gastric motility produced by administration of trichothecenes such as DON would therefore be obvious in view of the teaching of Arnold in view of Williams.*" (Office Action at page 7, emphasis added).

Arnold describes a short-term feeding study of rats fed a diet supplemented with varying concentrations of DON to determine the effect of DON on body weight, feed consumption, and several hematological parameters. Arnold describes a variable effect of DON on feed consumption and weight gain:

> "Body weight and feed consumption for treated male and female rats were significantly different ($p < 0.01$) from those of their corresponding controls. Control males gained weight more rapidly and consumed more feed, particularly during the first 3 weeks of the study. However, treated males in the 0.25 and 0.5 mg/kg groups experienced partial recovery in body weight and showed *significantly higher weight gain than controls* toward the middle of the study. *Body weight gain to feed consumption ratios only partially explained these weight gain differences.* For the duration of the study, only the 1 mg/kg males, and all of the treated female groups had reduced weekly body weight gains. The reduced body weights appeared to be due primarily to suppressed feed consumption." (page 693, Arnold; emphasis added).

The above excerpt shows that some of the treated male rats at times exhibited a *greater* weight gain than the controls. The reason for the results in the male rats remained a mystery and did not detract the investigators from focusing on toxic effects as others in the field had found. For example, in discussing the feeding study, Arnold noted that the results in female rats indicated that the effective dose for observing a toxic effect of DON was lower than in a previous study:

> "In our previous studies with diets containing wheat naturally contaminated with DON using rats and mice or with DON administered by gavage to mice, the apparent NOEL [no observable effect level] was somewhat below 1 mg/kg body wt [citation omitted]. However, in the present study the apparent NOEL *regarding the toxicological manifestations of DON* upon body weight, feed consumption and hematological parameters

> would appear to be less than 0.25 mg/kg body wt for the female rat . . . ." (page 694, Arnold; bracket comments and emphasis added).

Consistent with the rest of the mycotoxin literature, Arnold concluded that DON is an undesirable toxic substance that should continue to be studied:

> "Based on the results of this and previous experiments, more studies are required to: (1) ascertain the mechanism by which DON elicits *its toxicological effects*; and (2) attain a better understanding of the *toxicological consequences of DON ingestion by humans* of various ages." (page 695, Arnold; emphasis added).

Nowhere does Arnold indicate that any animal was treated for obesity in the feeding study. Only Applicants' specification discloses that pure preparations of DON and other trichothecenes or derivatives thereof possess a defined beneficial pharmacological activity of inducing a fed pattern of gut motility and that such compounds may be used therapeutically to treat obesity. Accordingly, the toxic or negative effect from ingesting the DON containing diet in Arnold is clearly *not* "equivalent to" or suggestive of Applicants' claimed method of treating obesity in humans and other vertebrate animals.

Applicants have explained the deficiencies of Williams above. Williams reviews various toxicological studies of the T-2 mycotoxin trichothecene. Although there is no basis in either document for combining Arnold and Williams, even if taken together, the combination of Arnold and Williams still fails to teach or suggest any beneficial pharmacological activity in DON or any other trichothecene or that such compounds may be used in Applicants' claimed method of treating obesity. Accordingly, the combination of Arnold and Williams fails to anticipate or make obvious Applicants' claimed invention.

Friend and Williams

Regarding the combination of Friend and Williams, the Examiner applied the same basic reasoning used above for rejecting the claims as anticipated by or obvious over the combination of Bergsjo and Williams and the combination of Arnold and Williams:

> "Friend et al disclose that exposure to DON (vomitoxin) reduces weight gain in pigs (See page 773, last paragraph). *This is equivalent to a treatment of obesity.* Further, the effects of T-2 mycotoxin such as trichothecene is well known as an inherent

> property of that molecule. In the alternative, this property of trichothecenes on gastric motility is disclosed by Williams et al at page 374. Williams also draws an equivalence between clinical symptoms in humans, cattle, swine and bird. The Fusarium mycotoxin is listed and is inclusive of DON (see Friend et al.). As such the instant method is clearly anticipated by Friend et al if the effects of gastric motility are viewed as an inherent property of that molecule. If in the alternative, it is not viewed as inherent, those of ordinary skill would expect similar decreases in weight as well as gastric motility effects in humans, cattle, pigs or birds given the disclosure of Friend et al in view of Williams. The treatment of obesity and effects on gastric motility produced by administration of trichothecenes such as DON would therefore be obvious in view of the teaching of Friend et al in view of Williams." (Office Action at pages 7-8, emphasis added.)

Friend describes a feed study in which pigs were fed a wheat-corn control diet ("CW"), a diet containing naturally contaminated wheat as a source of DON and uncontaminated (clean) corn ("VW"), or a diet containing clean wheat and corn that had been artificially inoculated with a strain of *Fusarium graminearum* as a source of DON ("IC"). The objectives of the study in Friend were:

> "(a) to determine sex differences in response to the feeding of DON-contaminated diets to boars (entire males) and gilts (entire females) and (b) to compare the effect on feed intake and weight gain of feeding naturally contaminated wheat and artificially (inoculated) contaminated corn as two different dietary sources of DON-contaminated grain." (pages 766-767, Friend).

Animals fed the fungally contaminated diets showed a decreased feed intake and weight gain, although there was considerable variation between animals and groups (see, in Friend, Abstract, page 765; Figure 1 (body weight), page 769; Figure 2 (feed intake), page 771). In fact, animals fed the fungally contaminated diets initially avoided the feed diet, a response often reported in the mycotoxin literature as being associated with an intense dissatisfaction of the test diet containing fungally-contaminated feed (see, e.g., second column,, page 770, in Friend; page 292 in Bergsjo). Typical of such studies employing fungally contaminated feed, Friend could not rule out the possibility that factors or substances other than DON may have been involved, and

particularly with respect to differences seen between pigs fed the two fungally contaminated diets:

> "On the basis of the chemical analyses, there is no explanation for these differences in response to diets VW and IC containing approximately the same DON concentrations and negligible concentrations of some other trichothecene mycotoxins know to have some clinical effects in common with DON. This phenomenon is certainly not without parallel . . . Our results suggest the presence of metabolites other than DON, associated with the inoculated corn diet, affecting the growth potential of these pigs." (page 770, Friend).

Applicants note, again, that the uncertainty expressed by Friend is representative of much of the traditional teachings of the mycotoxin literature. Nowhere does Friend teach or suggest that DON or any other trichothecene has a pharmacological activity to induce a fed pattern of gut motility or that such trichothecenes may be used beneficially to treat a disorder such as obesity. Nowhere does Friend mention that pigs were obese or benefited from consumption of the fungally contaminated wheat or corn. Accordingly, the study in Friend is clearly *not* "equivalent to" or suggestive of Applicants' claimed method of treating obesity.

Applicants have explained the deficiencies of Williams above. Williams reviews various toxicological studies of the T-2 mycotoxin trichothecene. Although there is no basis in either document for combining Friend and Williams, even if taken together, the combination of Friend and Williams still fails to teach or suggest any beneficial pharmacological activity in DON or any other trichothecene or that such compounds may be useful in Applicants' claimed method of treating obesity. Accordingly, the combination of Arnold and Williams fails to anticipate or make obvious Applicants' claimed invention.

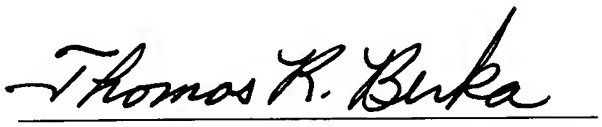
Applicants note here that the Examiner also cited D'Mello as a disclosure of serious side effects caused by *Fusarium* mycotoxins. D'Mello states that *Fusarium* mycotoxins include not only trichothecenes, but also a variety of other non-trichothecene compounds, e.g., zearalenone ("ZEN") and fumonisins, that have various harmful activities. D'Mello also mentions that the co-occurrence of known and unknown mycotoxins may have additive, synergistic, and/or "potentiating" interactions that result in harmful effects on livestock health and productivity.

D'Mello speculates that crops resistant to *Fusarium* infection offers the most viable strategy for reducing mycotoxin contamination of grain and animal feed.

The documents cited by the Examiner are all examples of the mycotoxin literature that only portrays DON and other trichothecenes as toxic substances that have no beneficial activity, but rather have detrimental effects on livestock and humans, and that should be avoided in food and feed sources. Such documents also illustrate the problems and uncertainty in this literature, e.g., in identifying the specific compound(s) or source(s) responsible for various and inconsistent pathologies, and particularly when a variety of different types and qualities of animals are fed various naturally or deliberately fungally contaminated crops as the source of a particular trichothecene of interest (e.g., as reported in Bergsjo and Friend). Each of the primary references (Bergsjo, Arnold, and Friend) notes inconsistencies between studies employing various sources of trichothecenes. The only consistent teaching of the documents cited by the Examiner is that trichothecenes are toxins that are detrimental to animals and that have no beneficial use. Applicants also note that weight loss *per se* is clearly of import in the mycotoxin literature *only* in the context of marketable weight of livestock, such as cattle and pigs. Nowhere is there any recognition of or suggestion that trichothecenes may be employed beneficially to control food intake and treat obesity. Only Applicants' specification provides the analytical, pharmacological, and neurophysiological data and teachings that trichothecenes such as DON act as neuroregulatory agents outside the gut to induce a fed pattern of gut motility that signals satiety to stop or reduce food intake and that such compounds may be used beneficially and safely to treat obesity. As none of the documents cited by the Examiner mentions or suggests such use of trichothecenes or derivatives thereof, Applicants' claimed invention is a new use for trichothecenes and derivative compounds and as such is patentable subject matter under 35 USC 101 and 102 and non-obvious in accordance with 35 USC 103. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejections.

In view of the foregoing remarks and the above amendment to the claims, Applicants submit that the rejections are rendered moot or have been overcome. Accordingly, Applicants respectfully request that the Examiner enter the amendment, withdraw the rejections, and pass Claims 1-7 to allowance.

Respectfully submitted,



Thomas R. Berka, Ph.D. (Reg. No. 39,606)
Leon R. Yankwich (Reg. No. 30,237)
Attorneys for Applicants
YANKWICH & ASSOCIATES, P.C.
201 Broadway
Cambridge, Massachusetts 02139
telephone: (617) 374-3700
fax: (617) 374-0055

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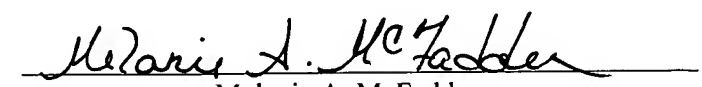

Melanie A. McFadden